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Clinical Outcomes by Sex After Pulsed Field Ablation of Atrial Fibrillation

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IMPORTANCE Previous studies evaluating the association of patient sex with clinical outcomes using conventional thermal ablative modalities for atrial fibrillation (AF) such as radiofrequency or cryoablation are controversial due to mixed results. Pulsed field ablation (PFA) is a novel AF ablation energy modality that has demonstrated preferential myocardial tissue ablation with a unique safety profile.

OBJECTIVE To compare sex differences in patients undergoing PFA for AF in the Multinational Survey on the Methods, Efficacy, and Safety on the Postapproval Clinical Use of Pulsed Field Ablation (MANIFEST-PF) registry.

DESIGN, SETTING, AND PARTICIPANTS This was a retrospective cohort study of MANIFEST-PF registry data, which included consecutive patients undergoing postregulatory approval treatment with PFA to treat AF between March 2021 and May 2022 with a median follow-up of 1 year. MANIFEST-PF is a multinational, retrospectively analyzed, prospectively enrolled patient-level registry including 24 European centers. The study included all consecutive registry patients (age ≥18 years) who underwent first-ever PFA for paroxysmal or persistent AF.

EXPOSURE PFA was performed on patients with AF. All patients underwent pulmonary vein isolation and additional ablation, which was performed at the discretion of the operator.

MAIN OUTCOMES AND MEASURES The primary effectiveness outcome was freedom from clinically documented atrial arrhythmia for 30 seconds or longer after a 3-month blanking period. The primary safety outcome was the composite of acute (<7 days postprocedure) and chronic (>7 days) major adverse events (MAEs).

RESULTS Of 1568 patients (mean [SD] age, 64.5 [11.5] years; 1015 male [64.7%]) with AF who underwent PFA, female patients, as compared with male patients, were older (mean [SD] age, 68 [10] years vs 62 [12] years; $P < .001$), had more paroxysmal AF (70.2% [388 of 553] vs 62.4% [633 of 1015]; $P = .002$) but had fewer comorbidities such as coronary disease (9% [38 of 553] vs 15.9% [129 of 1015]; $P < .001$), heart failure (10.5% [58 of 553] vs 16.6% [168 of 1015]; $P = .001$), and sleep apnea (4.7% [18 of 553] vs 11.7% [84 of 1015]; $P < .001$). Pulmonary vein isolation was performed in 99.8% of female (552 of 553) and 98.9% of male (1004 of 1015; $P = .90$) patients. Additional ablation was performed in 22.4% of female (124 of 553) and 23.1% of male (235 of 1015; $P = .79$) patients. The 1-year Kaplan-Meier estimate for freedom from atrial arrhythmia was similar in male and female patients (79.0%; 95% CI, 76.3%-81.5% vs 76.3%; 95% CI, 72.5%-79.8%; $P = .28$). There was also no significant difference in acute major AEs between groups (male, 1.5% [16 of 1015] vs female, 2.5% [14 of 553]; $P = .19$).

CONCLUSION AND RELEVANCE Results of this cohort study suggest that after PFA for AF, there were no significant sex differences in clinical effectiveness or safety events.

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Invited Commentary

Supplemental content

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The role of sex in determining the risks and benefits of catheter ablation for atrial fibrillation (AF) is controversial because there are important differences in the incidence, presentation, and management of AF between male and female individuals.[1,2] Previous studies evaluating the association of sex with clinical outcomes using conventional AF thermal-ablative modalities such as radiofrequency or cryoablation are controversial due to mixed results.[2-13] Potential explanations for this disparity include the following: (1) a more complex clinical profile including older age in female individuals, (2) a greater number of comorbidities, (3) smaller left atria and thinner atrial walls, which can render the procedure to be more technically difficult, (4) longer AF duration due to delayed or less frequent referral for catheter ablation, (5) greater incidence of nonparoxysmal AF, (6) more extensive atrial fibrosis, and (7) a higher prevalence of non-pulmonary vein triggers in female individuals.[6,14-16]

Pulsed field ablation (PFA) is a novel, nonthermal cardiac ablation energy modality that, in preclinical studies, has demonstrated preferential myocardial tissue ablation by irreversible electroporation.[17-28] Importantly in clinical trials, PFA has demonstrated a unique safety profile, with no reported instances of pulmonary vein stenosis or evidence of esophageal injury.[29-34] Beyond the favorable safety profile, the first in-human PFA trials demonstrated an effectiveness ranging from 55% to 92% at 1 year depending on AF type, PFA technology used, and intensity of AF monitoring.[31,34-36]

Multinational Survey on the Methods, Efficacy, and Safety on the Postapproval Clinical Use of Pulsed Field Ablation (MANIFEST-PF) is a large patient-level registry that includes the first 24 centers that commenced the clinical use of PFA for the treatment of AF after regulatory approval in Europe. MANIFEST-PF includes the largest cohort of female patients treated with PFA and offers an important resource for assessing clinically important sex-based differences in response to PFA.

Key Points

Question Is patient sex associated with differences in clinical outcomes of pulsed field ablation (PFA) for the treatment of patients with atrial fibrillation (AF)?

Findings In this large cohort study using a patient-level registry including 1568 consecutive patients who underwent PFA for paroxysmal or persistent AF, there was no significant difference between male and female patients in the 1-year freedom from recurrent atrial arrhythmia or major adverse events.

Meaning Results suggest that there was no association between patient sex and clinical outcomes of PFA as similar outcomes were observed by sex at 1-year follow-up after PFA for treatment of AF.

Methods

Study Population

All patients in the MANIFEST-PF registry were included in this study. MANIFEST-PF was a retrospective analysis, conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee at Homolka Hospital. A waiver of consent was granted by the ethical committee due to the use of deidentified personal information. As previously described, MANIFEST-PF is a large multinational registry from 24 European centers, including patients (aged 18 years and older) who underwent first-ever PFA for paroxysmal AF, persistent AF, or long-standing persistent AF after regulatory approval in March 1, 2021, enrolling consecutive patients in approximately May 2022.[37] Patients were categorized by sex (male vs female) and evaluated for clinical outcomes of PFA within sex subgroups, including freedom from AF and adverse events. Participant race and ethnicity information was not collected as these data were not considered relevant to this analysis. Participating centers and additional author disclosures, respectively, are available in eAppendix 1 and 2 in Supplement 1. The results are reported based on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Pulsed Field Ablation

Details of the treatment strategies and follow-up in the MANIFEST-PF registry have been previously described.[37] During PFA, a series of high-voltage, ultrashort electric pulses are delivered to the targeted area. These pulses create microscopic pores in the cell membranes of the cardiac tissue cells (electroporation), disrupting their function and leading to apoptosis. Among cell types, myocardial cells have the lowest thresholds to these electric fields, potentially permitting preferential myocardial ablation.

Briefly, patients underwent preablation transesophageal echocardiography or contrast-enhanced computed tomography, or intraprocedural intracardiac echocardiography (ICE), to rule out left atrial appendage thrombus. PFA was performed under moderate sedation or general anesthesia with endotracheal intubation. Electroanatomic mapping and ICE were performed at the operator's discretion. Ablation was performed by sequentially positioning the PFA catheter (Farawave [Boston Scientific Inc]) at each pulmonary vein (PV) ostium to deliver a series of applications in basket and flower orientations. Patients typically received PFA based on a standard protocol; 2 applications were delivered for each PV in a basket pose, then the basket was rotated approximately 36° to change the spline orientation, and another 2 applications were delivered. The same algorithm was repeated using the flower pose to extend the level of PV isolation (PVI). All patients underwent PVI, defined by entrance block as confirmed by the absence of electrograms. Isoproterenol or adenosine was administered at physician discretion. In patients with persistent AF and long-standing persistent AF, ancillary ablation included ablation of the posterior wall, roof, mitral isthmus, cavotricuspid isthmus, and other ablations were performed either with PFA or a commercially available radiofrequency ablation catheter at the operator's discretion. The treating physician made the decision about the use of antiarrhythmic drugs (AADs). Oral anticoagulation therapy was typically in accordance with current AF guidelines.

Scheduled patient follow-up was performed at 3, 6, and 12 months, with assessments for AF-associated symptoms,

major or minor adverse events, and 12-lead ECGs or 24-hour Holter monitoring, as per physician discretion.

Primary and Secondary Clinical Outcomes

The primary effectiveness outcome in the MANIFEST-PF registry was freedom from documented atrial arrhythmia (AF, atrial flutter, or atrial tachycardia) outside the 90-day blanking period, lasting 30 seconds or longer irrespective of symptoms with or without AADs. The secondary effectiveness outcome was freedom from atrial arrhythmia outside the 90-day blanking period lasting 30 seconds or longer plus freedom from class I or III AADs or reablation.

The primary safety outcome included the composite of acute (<7 days postprocedure) and chronic (>7 days postprocedure) major adverse events. Major adverse events included atrioesophageal fistula, symptomatic pulmonary vein stenosis, cardiac tamponade/perforation requiring intervention or surgery, stroke or systemic thromboembolism, persistent phrenic nerve injury, vascular access complications requiring surgery, coronary artery spasm, and death. Minor adverse events included pericardial effusion without intervention, pericarditis, air embolism, transient ischemic attack (TIA), transient phrenic nerve injury, vascular complications not requiring surgery, deep vein thrombosis, and respiratory-related complications.

Statistical Analysis

Descriptive characteristics are reported as mean (SD) or median (IQR) values for continuous variables (based on normality distribution) and counts or percentages for categorical variables. Comparisons between groups were performed using *t* tests or the Mann-Whitney *U* test for continuous variables and Pearson χ^2 test or Fisher exact test for categorical variables. A propensity score–matched analysis was performed for those baseline characteristics that typically affect AF ablation outcomes: age, body mass index (BMI), coronary artery disease, heart failure, hypertension, sleep apnea, and diabetes. The primary and secondary effectiveness outcomes were estimated using the Kaplan-Meier method, and survival curves were compared using the log-rank test. Baseline characteristics were examined in the univariate analysis, with the primary effectiveness outcome of atrial arrhythmia recurrence as the dependent variable. Variables with $P < .10$ in the univariate analysis were included in a multivariate Cox model. Multiple imputations were performed to account for missing data. Cox proportional hazards models were used to identify factors associated with primary effectiveness failure, with an estimation of the hazard ratio (HR) and 95% CI. All tests were 2-tailed, and *P* values < .05 indicated statistical significance. All statistical analyses were performed using the SPSS software, version 29.0 (IBM Corp).

Results

Baseline Characteristics

The MANIFEST-PF registry included 1568 patients (mean [SD] age, 64.5 [11.5] years; 1015 male [64.7%]; 553 female [35.3%]) with AF who underwent PFA (**Table 1**). On average, female patients as compared with male patients were older (mean [SD] age, 68 [10] years vs 62 [12] years; $P < .001$) and had more paroxysmal AF (70.2% [388 of 553] vs 62.4% [633 of 1015]; $P = .002$) but fewer comorbidities such as coronary disease (9% [38 of 553] vs 15.9% [129 of 1015]; $P < .001$), heart failure (10.5% [58 of 553] vs 16.6% [168 of 1015]; $P = .001$), and sleep apnea (4.7% [18 of 553] vs 11.7% [84 of 1015]; $P < .001$). In addition, female patients were less likely to have persistent AF than male patients (27.1% [150 of 553] vs 34.3% [348 of 1015]). The prevalence of hypertension, diabetes, chronic obstructive pulmonary disease, and previous stroke or TIA were similar between female and male individuals. There was no difference in the use of preablation class I and III AADs between groups. The baseline characteristics based on AF type between male and female individuals are shown in eTable 1 in Supplement 1.

Procedural Characteristics

A similar proportion of male and female individuals underwent PFA with endotracheal intubation, electroanatomic mapping, and ICE imaging (**Table 2**). PVI was successfully achieved in almost all patients (99.8% of female [552 of 553] and 98.9% of male [1004 of 1015]; $P = .90$). Additional ablation was performed in 22.4% of female (124 of 553) and 23.1% of male (235 of 1015; $P = .79$) patients. There were no significant differences in the use of adjunctive lesion sets between male and female individuals undergoing ablation for paroxysmal AF (15.2% [59 of 388] vs 12.1% [77 of 633]; $P = .22$) or persistent AF (39.3% [65 of 165] vs 41.3% [158 of 382]; $P = .77$). Female patients were more likely to undergo additional mitral isthmus ablation than male patients for persistent AF (7.9% [13 of 165] vs 3.1% [12 of 382]; $P = .02$) (eTable 2 in Supplement 1). The median (IQR) fluoroscopy (11 [6-17] minutes vs 14 [7-22] minutes; $P = .004$) and procedure times (60 [40-93] minutes vs 72 [48-103] minutes; $P = .002$) were shorter in female patients for persistent AF but not for paroxysmal AF ablation (eTable 2 in Supplement 1). The group of patients requiring a repeated ablation procedure constituted only a small subset of the full cohort (147 of 1568 patients [9.4%]). The likelihood of undergoing repeated ablation did not differ between the female and male patients (8.3% [46 of 553] vs 10.0% [101 of 1015]; $P = .32$).

Follow-Up

There was no significant difference in the median (IQR) number of follow-up visits (3 [2-3] visits vs 3 [2-3] visits; $P = .76$), 24-hour Holter monitoring (2 [1-3] vs 2 [1-3]; $P = .54$), and follow-up duration (367 [306-428] days vs 366 [279-420] days; $P = .40$) between the 2 groups (**Table 3**).

Primary and Secondary Effectiveness Outcomes

The primary effectiveness outcome of the 1-year Kaplan-Meier estimate for freedom from AF, atrial flutter, and atrial tachycardia after a single procedure was similar between groups (female: 76.3%; 95% CI, 72.5%-79.8% vs male: 79.0%; 95% CI, 76.3%-81.5%; $P = .28$). Compared with male patients, there was no significant difference in the median (IQR) time to the first

Table 1. Baseline Characteristics

Characteristics	No. (%) of patients with available data	Entire cohort (N = 1568)	Female patients (n = 553)	Male patients (n = 1015)	*P* value
Age, mean (SD), y	1568 (100)	64.5 (11.5)	68.2 (10.3)	62.5 (11.6)	<.001
AF type, No. (%)					
Paroxysmal	1568 (100)	1021 (65)	388 (70.2)	633 (62.4)	.002
Persistent	1568 (100)	498 (32)	150 (27.1)	348 (34.3)	.03
Long-standing persistent	1568 (100)	49 (3)	15 (2.7)	34 (3.3)	.50
CHA_2DS_2-VASc, mean (SD)	1568 (100)	2.2 (1.6)	3.0 (1.5)	1.8 (1.5)	<.001
Medical history					
Body mass index, mean (SD)	1554 (99.1)	28 (5)	27.7 (5.7)	28.2 (4.5)	.051
Atrial flutter, No. (%)	1235 (78.8)	158 (12.8)	43 (10.1)	115 (14.2)	.05
Coronary artery disease, No. (%)	1235 (78.3)	167 (13.5)	38 (9.0)	129 (15.9)	<.001
Diabetes, No. (%)	1568 (100)	196 (12.5)	71 (12.8)	125 (12.3)	.81
Hypertension, No. (%)	1568 (100)	959 (61.1)	348 (62.9)	611 (60.2)	.30
Heart failure, No. (%)	1568 (100)	226 (14.4)	58 (10.5)	168 (16.6)	.001
Sleep apnea, No. (%)	1104 (70.4)	102 (9.2)	18 (4.7)	84 (11.7)	<.001
Prior stroke/TIA, No. (%)	1568 (100)	97 (6.2)	34 (6.1)	63 (6.2)	>.99
COPD, No. (%)	992 (63.3)	50 (5)	18 (5.3)	32 (4.9)	.76
Echocardiographic parameters					
LVEF, median (IQR), %	1381 (88.1)	60 (55-64)	60 (55-65)	60 (54-63)	.01
LA diameter, median (IQR), mm	1220 (77.8)	42 (39-46)	42 (38-45)	42 (39-46)	<.001
Antiarrhythmic medications					
Class I AADs (%)	1566 (99.9)	343 (21.9)	129 (23.3)	214 (21.1)	.34
Class III AADs (%)	1567 (99.9)	279 (17.8)	95 (17.2)	184 (18.1)	.68

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age, sex category; COPD, chronic obstructive pulmonary disease; LA, left atrium; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

Table 2. Procedural Characteristics

Procedure characteristics	No. (%)[a]				*P* value
	No. of patients with available data	Entire cohort (N = 1568)	Female patients (n = 553)	Male patients (n = 1015)	
Intubation	1568 (100)	317 (20)	108 (19.5)	209 (20.6)	.65
Mapping	1568 (100)	457 (29)	152 (27.5)	305 (30.1)	.29
ICE imaging	1234 (79)	407 (33)	145 (34.2)	262 (32.3)	.52
Ablation lesion sets					
Acute PV isolation	1568 (100)	1556 (99.2)	552 (99.8)	1004 (98.9)	.90
Additional non-PV ablation	1568 (100)	359 (22.8)	124 (22.4)	235 (23.1)	.79
Posterior wall ablation	1568 (100)	173 (11)	55 (10.0)	118 (11.6)	.36
Mitral line	1568 (100)	37 (2.4)	21 (3.8)	16 (1.6)	.008
CTI line	1568 (100)	84 (5.4)	24 (4.3)	60 (5.9)	.20
Roof line	1568 (100)	21 (1.3)	8 (1.4)	13 (1.3)	.82
Other ablation	1568 (100)	44 (2.8)	16 (2.9)	28 (2.8)	.87
Type of energy used to perform additional ablation					
Pulsed field energy	359 (100)	305 (85)	111 (20.1)	194 (19.1)	.71
Radiofrequency	359 (100)	54 (15)	13 (2.3)	41 (4.0)	.09
Fluoroscopy time, median (IQR), min	1521 (97.0)	12 (7-19)	11.0 (6.6-17.2)	12.0 (7.0-19.4)	.05
Procedure time, median (IQR), min	1540 (98.2)	61 (40-90)	57.0 (40.0-87.5)	65 (42.0-92.0)	.002
Same day discharge	1234 (78.7)	101 (6.4)	37 (8.7)	64 (7.9)	.66

Abbreviations: CTI, cavotricuspid isthmus; ICE, intraprocedural intracardiac echocardiography; PV, pulmonary vein.

[a] Values listed as No. (%) unless otherwise specified.

AF recurrence in female patients (176 [126-253] days vs 183 [130-296] days; *P* = .21). Clinical effectiveness was higher for paroxysmal AF (female: 80.2% [75.8%-84.0%] vs male: 82.5% [79.2%-85.3%]; *P* = .30) than for persistent AF/long-standing persistent AF (female: 67.3% [59.5%-74.3%] vs male: 73.3% [68.5%-77.7%]; *P* = .40) but similar in both sexes (**Figure**).

Table 3. Effectiveness Outcomes

Effectiveness outcomes	No. (%)[a] Entire cohort (N = 1568)	Female patients (n = 553)	Male patients (n = 1015)	P value
Primary effectiveness outcome				
Freedom from AF/AFL/AT	1224 (78.1)	422 (76.3)	802 (79.0)	.28
Secondary effectiveness outcome				
Freedom from AF/AFL/AT not taking AADs or repeated ablation	1110 (70.8)	376 (68.0)	734 (72.3)	.10
Follow-up duration, median (IQR), d	367 (289-421)	367 (306-428)	366 (279-420)	.40
No. of follow-up 24-h Holter monitors, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	.54
No. of follow-up visits, median (IQR)	3 (2-3)	3 (2-3)	3 (2-3)	.76
Time to AF/AFL recurrence, median (IQR), d	180 (129-266)	183 (130-296)	176 (126-253)	.21
Repeated ablation	147 (9.3)	46 (8.3)	101 (10.0)	.32

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia.

[a] Values listed as No. (%) unless otherwise specified.

The secondary effectiveness outcome of the 1-year Kaplan-Meier estimate for freedom from atrial arrhythmias without AADs or repeated ablation was also similar between groups (female: 68.0%; 95% CI, 63.9%-71.9% vs male: 72.3%; 95% CI, 69.4%-75%; *P* = .10) (eFigure 1 in Supplement 1). However, secondary clinical effectiveness was higher in male compared with female individuals in patients with paroxysmal AF (75.7%; 95% CI, 79.2%-85.3% vs 70.9%; 95% CI, 75.8%-84.0%; *P* = .04) and similar in patients with persistent AF/long-standing persistent AF (66.8%; 95% CI, 61.8%-71.4% vs 61.2%; 95% CI, 53.3%-68.7%; *P* = .59) (eFigure 2 in Supplement 1).

Risk Factors Associated With Primary and Secondary Effectiveness Outcomes

Multivariable Cox regression modeling was performed to identify potential risk factors associated with primary and secondary effectiveness failure (eTables 3-6 in Supplement 1). Primary effectiveness failure was associated with persistent AF (HR, 1.34; 95% CI, 1.05-1.70; *P* = .02), left ventricular ejection fraction (LVEF; HR, 0.98; 95% CI, 0.97-1.00; *P* = .047), left atrium (LA) diameter (HR, 1.02; 95% CI, 1.01-1.03; *P* = .004), and procedure time (HR, 1.00; 95% CI, 1.00-1.01; *P* = .04) (eTable 5 in Supplement 1), whereas secondary effectiveness failure was associated with LVEF (HR, 0.98; 95% CI, 0.97-0.99; *P* = .004) and LA diameter (HR, 1.02; 95% CI, 1.01-1.03; *P* = .007) (eTable 6 in Supplement 1). Female sex was not a risk factor of failure of primary or secondary effectiveness. These clinical risk factors remained consistent in both paroxysmal and persistent AF cohorts.

In the 553 female patients in the MANIFEST-PF registry, the clinical variables that were associated with primary effectiveness failure were history of persistent AF (HR, 2.2; 95% CI, 1.21-3.97; *P* = .01) and LA diameter 45 mm or greater (HR, 2.23; 95% CI, 1.32-3.90; *P* = .003) (eFigure 3 in Supplement 1).

Safety Outcomes

The overall rate of adverse events was low, with major adverse events occurring in 2.5% of female (14 of 553) and 1.5% of male (16 of 1015; *P* = .19) (**Table 4**) patients. There have been no reports of PFA-associated symptomatic PV stenosis or esophageal complications, including atrioesophageal fistula, esophageal ulcerations, or esophageal dysmotility in either group. Transient phrenic nerve injury occurred in 0.2% of female (1 of 553) and 0.5% of male (5 of 1015; *P* = .67) patients, whereas persistent phrenic nerve injury occurred in 1 female (0.2%) and in no male patients. Coronary spasm (female, 0.2% [1 of 553]; male, 0.1% [1 of 1015]) and vascular access complications requiring surgery (female, 0.2% [1 of 553]; male, 0.1% [1 of 1015]) were rare in both sexes.

Complications associated with catheter manipulation, such as cardiac tamponade, occurred in 1.4% of female (8 of 553) and 1.0% of male (10 of 1015; *P* = .46) patients. Stroke rates were similar in both sexes, occurring in 0.4% of female patients (2 of 553), with 1 stroke resulting in death, and in 0.4% of male patients (4 of 1015; *P* > .99).

There was also no significant difference in the incidence of acute minor adverse events (female, 3.1% [17 of 553] vs male, 4.5% [46 of 1015]; *P* = .17) between groups. Most of these were vascular complications that were conservatively managed.

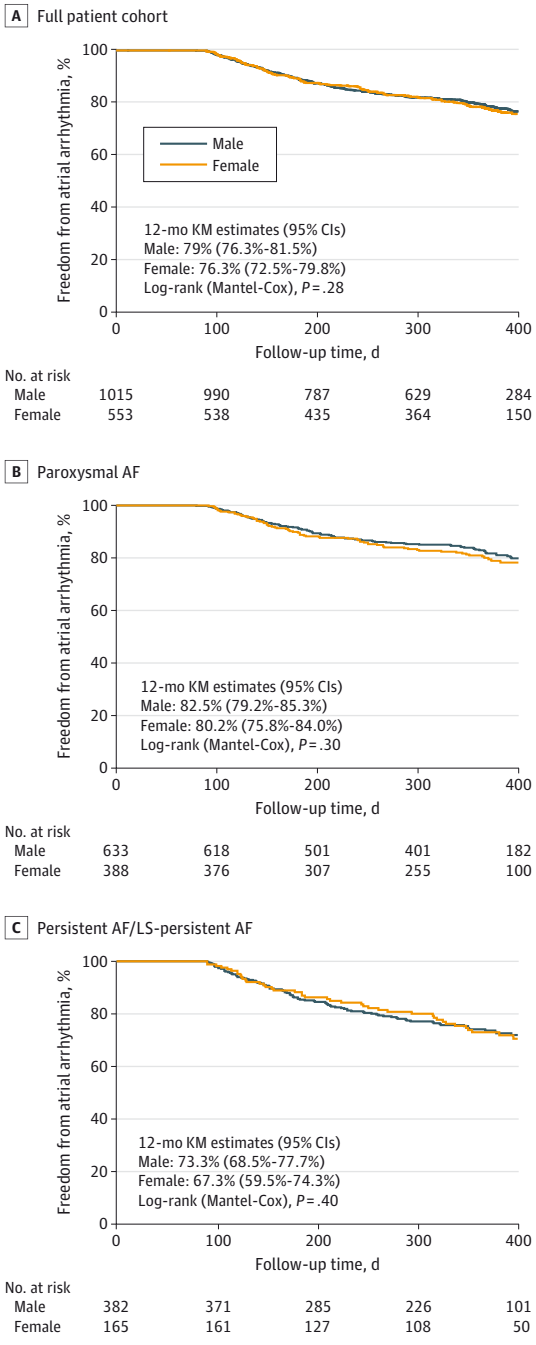
Outcomes From Repeated Ablation Procedures

Of the 344 patients with recurrence of atrial arrhythmia after the index PFA procedure, at least 1 repeated procedure was performed in 147 patients (42.7%). Of these patients, 8.3% (46 of 553) were female and 10.0% (101 of 1015) were male (*P* = .32). Among the patients who underwent repeat ablation, per-vein durability was similar between female and male individuals (82.6% [152 of 184] vs 68.1% [275 of 404], respectively; *P* = .15), but per-patient PVI durability was significantly higher in female than male individuals (63.0% [29 of 46] vs 37.8% [38 of 101], respectively; *P* = .005) (eFigure 4 in Supplement 1).

Propensity Score-Matched Population

The propensity-matched cohort included 730 patients (365 male, 365 female). The mean (SD) age was 66.5 (9.5) years, the mean (SD) BMI was 27.8 (4.9; calculated as weight in kilograms divided by height in meters squared), and the mean (SD) CHA_2DS_2-VASc score was 2.2 (1.6). The CHA_2DS_2-VASc score assesses risk in AF and stands for congestive heart failure, hypertension, age, diabetes, prior stroke or TIA or thromboembolism, vascular disease, age, and sex category. After propensity matching for risk factors, including age, BMI, coro-

Figure. Kaplan-Meier (KM) Analysis of Freedom From Atrial Arrhythmia by Sex



The primary effectiveness outcomes are shown for both the full patient cohort (A) and separated by atrial fibrillation (AF) subtype: paroxysmal AF (B) vs persistent AF/long-standing (LS)–persistent AF (C).

nary artery disease, diabetes, hypertension, heart failure, and sleep apnea, female patients had a higher prevalence of paroxysmal AF (70.1% [256 of 365] vs 57.8% [211 of 365]; $P < .001$), whereas male patients had a higher prevalence of persistent AF (38.4% [140 of 365] vs 27.9% [102 of 365]; $P = .03$) and a larger median (IQR) LA diameter (43 [40-47] mm vs 42 [38-45] mm; $P < .001$). Other baseline characteristics were similar between sexes in the propensity-matched cohort (eTable 7 in Supplement 1).

In the propensity-matched cohorts, there was again no difference in AF recurrence between sexes for either paroxysmal or persistent AF (eFigures 5 and 6 in Supplement 1). A multivariate Cox regression analysis was performed including age, female sex, BMI, history of persistent AF, diabetes, hypertension, heart failure, sleep apnea, CHA_2DS_2-VASc score, LVEF, LA diameter, PVI plus ablation, and procedure time. Persistent AF (HR, 2.1; 95% CI, 1.37-3.22; $P < .001$) and LA diameter (HR, 1.04; 95% CI, 1.02-1.06; $P < .001$) were associated with primary effectiveness failure (eTable 8 in Supplement 1).

Discussion

MANIFEST-PF is a large registry including 1568 patients with AF who underwent first-time catheter ablation using pulsed field energy in both male and female individuals. The registry provides, to our knowledge, the largest comparison of sex outcomes using PFA, and one of the largest using any ablation modality. The main findings are as follows: (1) there was no significant difference in the primary effectiveness outcome of 1-year recurrence of atrial arrhythmia between male and female patients (79.0% vs 76.3%; $P = .28$), (2) repeated ablation rates (male: 8.3% vs female: 10.0%; $P = .32$) were similar between sexes, (3) among the patients who underwent repeated ablation, PVI durability was higher in female than in male patients (per vein, 82.6% vs 68.1%; $P = .15$ and per patient, 63.0% vs 37.8%; $P = .005$), and (4) procedure-associated adverse events were low and did not differ significantly by sex (female: 2.5% vs male: 1.5%; $P = .19$).

Clinical Effectiveness

MANIFEST-PF demonstrated similar clinical effectiveness with PFA in both male and female individuals for both paroxysmal and persistent AF. The primary effectiveness outcome of freedom from atrial arrhythmia recurrence (>30 seconds after blanking) was 79.0% in male patients and 76.3% in female patients at 12 months of follow-up, with greater overall effectiveness in the paroxysmal AF cohort (male: 82.5% vs female: 80.2%; $P = .30$) than in the persistent AF/long-standing persistent AF cohort (male: 73.3% vs female: 67.3%; $P = .40$). These effectiveness rates compare favorably with early clinical experience with PFA.[31,32,34,36] However, none of the previous studies examining PFA for AF reported clinical outcomes according to sex.

Previous studies using conventional thermal ablation technologies such as radiofrequency or cryoablation showed mixed results in ablation effectiveness between male and female individuals.[1,3,8,12,13] An analysis from the 750-patient Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation (FIRE AND ICE) trial, using both radiofrequency or cryoablation, showed that female sex was associated with a 37% increase in risk of AF recurrence compared with male sex.[3] In the Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest

Table 4. Major and Minor Adverse Events

Safety outcomes	No. (%)			*P* value
	Entire cohort (N = 1568)	Female patients (n = 553)	Male patients (n = 1015)	
Acute major adverse events	30 (1.9)	14 (2.5)	16 (1.5)	.19
Esophageal fistula	0	0	0	NA
Symptomatic PV stenosis	0	0	0	NA
Cardiac tamponade	18 (1.1)	8 (1.4)	10 (1.0)	.46
Percutaneous drainage	14 (0.8)	5 (1.2)	9 (1.1)	>.99
Surgical drainage	2 (0.1)	2 (0.5)	0	.11
Stroke	6 (0.4)	2 (0.4)	4 (0.4)	>.99
Coronary spasm	2 (0.1)	1 (0.2)	1 (0.2)	>.99
Phrenic nerve injury (persistent)	1 (0.06)	1 (0.2)	0	NA
Death	1 (0.06)	1 (0.2)	0	.35
Vascular complications requiring surgery	2 (0.1)	1 (0.2)	1 (0.2)	>.99
Acute minor adverse events	63 (4.0)	17 (3.1)	46 (4.5)	.17
Pericardial effusion without intervention	4 (0.3)	2 (0.5)	2 (0.5)	.61
Pericarditis	1 (0.06)	0	1 (0.1)	>.99
Air embolism	4 (0.3)	2 (0.4)	2 (0.4)	.61
TIA	2 (0.1)	1 (0.2)	1 (0.2)	>.99
Phrenic nerve injury, transient	6 (0.4)	1 (0.2)	5 (0.5)	.67
Vascular access complications	41 (2.6)	10 (1.8)	31 (3.1)	.18
Hematoma	33 (2.1)	6 (1.1)	27 (2.7)	.04
A-V fistula	5 (0.3)	2 (0.4)	3 (0.3)	>.99
Pseudoaneurysm	2 (0.1)	1 (0.2)	1 (0.1)	>.99
DVT	1 (0.06)	0	1 (0.1)	>.99
Respiratory related	4 (0.3)	1 (0.2)	3 (0.3)	>.99
Chronic major adverse events	0	0	0	NA

Abbreviations: A-V, arteriovenous; DVT, deep vein thrombosis; NA, not applicable; PV, pulmonary vein; TIA, transient ischemic attack.

Among Patients With Atrial Fibrillation (CABANA) trial subanalysis of 1108 patients undergoing radiofrequency ablation, 12-month AF recurrence was significantly reduced in patients undergoing ablation compared with those receiving drug therapy regardless of sex, but the effect was greater in male patients (HR, 0.48; 95% CI, 0.40-0.58) compared with female patients (HR, 0.64; 95% CI, 0.51-0.82; $P = .06$).[1] On the other hand, the Cryoballoon or Radiofrequency Ablation for Atrial Fibrillation Assessed by Continuous Monitoring (CIRCA-DOSE) substudy including 346 patients showed no significant difference in freedom from symptomatic atrial tachyarrhythmia at 1 year between male and female patients (79.1% vs 77.6%; $P = .92$).[13] Another recent single-center study including 1412 patients (radiofrequency ablation, 1349; cryoablation, 219) showed no increased risk of AF recurrence in female patients compared with male patients in both the full (HR, 1.15; 95% CI, 0.92-1.43; $P > .05$) and propensity-matched (HR, 1.08; 95% CI, 0.86-1.36; $P = .5$) cohorts.[38]

The exact mechanism(s) underlying any potential sex differences remain unclear. Putative explanations include a greater prevalence of non-PV triggers,[14,39] more advanced atrial disease, including low left atrial voltage, slower conduction and greater fractionated signals,[40] greater epicardial adipose tissue,[41] and a smaller decrease in parasympathetic activity after AF ablation[42] in female individuals. In addition, female individuals are prone to a series of inflammatory processes, including myofibroblast activation, oxidative stress, and cellular calcium overload, which are associated with atrial remodeling and AF progression.[43] Although information about AF triggers was not reported in MANIFEST-PF, there was no significant difference in the proportion of female patients compared with male patients who received additional non-PV ablation (22.4% vs 23.1%; $P = .79$); however, these lesions largely targeted substrate as opposed to triggers. The value of additional non-PV ablation for either paroxysmal or persistent AF remains uncertain, but it is certainly possible that female individuals may have more recurrences if specific triggers are not ablated.

However, among the subset of patients who underwent clinical repeated procedures, female patients had higher rates of PVI durability (per PV: 82.6% vs 68.1%; $P = .15$ and per patient: 63.0% vs 37.8%; $P = .005$). These findings of higher PVI durability in female patients compared with male patients have been previously described with radiofrequency ablation as well.[44] The reason for this difference in durability is unknown but possibly related to anatomic issues such as the left atrial size being somewhat smaller in female individuals. Of course, it is important to recognize that the group of patients requiring a repeated ablation procedure constituted only a small subset of the full cohort of 1568 patients (147 patients; 9.4%) and may not be fully representative of the full cohort. Thus, it is difficult to conclude that there was a hidden difference in sex outcomes that was offset by differential PVI durability rates.

Safety

In the MANIFEST-PF registry, the rate of major procedure-associated adverse events was low and consistent with other contemporary AF ablation studies using PFA[30,34,36] and did not differ significantly between the sex groups (female: 2.5% vs male: 1.5%). Major adverse events mostly consisted of cardiac tamponade (female: 1.4% vs male: 1.0%; $P = .46$) and stroke (0.4% vs 0.4%, $P > .99$). Importantly, there were no atrioesophageal fistulas or symptomatic PV stenosis in either sex. This is consistent with prior preclinical, first in-man clinical studies and real-world experience from the MANIFEST-PF registry, demonstrating the preferentiality of myocardial tissue susceptibility to PFA.[22,25,29-32,37]

Previous studies reporting the association of sex with AF ablation have been mixed with some studies reporting a higher risk of procedure-associated complications including cardiac tamponade, stroke/TIA, vascular complications, and major bleeding in female patients compared with male patients.[2-4,8,10,11,14] Potential explanations include the following: (1) smaller cardiac and venous structures in female individuals, making it difficult for venous access and catheter manipulation, (2) older age and greater comorbidity burden in female individuals undergoing AF ablation, (3) higher incidence of atrial fibrosis and non-pulmonary vein AF in female individuals requiring aggressive additional ablation, and (4) sex differences in genetic, hormonal, and thromboembolic factors.

The absence of sex differences for major adverse events in the MANIFEST-PF registry suggests the evolving safety of AF ablation procedures with improved transseptal puncture techniques, use of intracardiac echocardiography, advanced single-shot PFA technology that minimizes extensive catheter manipulation in the left atrium, and use of non-vitamin K oral anticoagulants.

Strengths and Limitations

This study's main strength is that MANIFEST-PF was a retrospective, nonrandomized comparative study, which, to our knowledge, was the largest PFA study to date and included multicenter patient-level data.

However, this study also has limitations. Despite extensive propensity-matched analysis and adjustment for multiple comorbidities, we cannot rule out the possibility that treatment selection and unmeasured confounders between sexes could affect the validity of the study findings. In addition, the median number of follow-up 24-hour Holter monitors used for AF monitoring was 2 (IQR, 1-3) and may have resulted in inaccurate estimates of AF recurrence rates and clinical effectiveness.

Conclusions

In this large, patient-level, observational registry of the first postapproval clinical use of PFA to treat AF, results suggest that there were no sex differences in clinical effectiveness or safety. The current data sets the stage for further studies using systematic, longer-term monitoring methods to confirm the effectiveness of PFA in male and female individuals.

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